WHAT IS CLAIMED IS:

1. An oral solid dosage form comprising a dose of unmodified insulin that achieves a comparable reduction in blood glucose concentration in human diabetic patients compared to a subcutaneous insulin injection in those patients, while providing a lower concentration of insulin in the peripheral blood circulation under acute, sub-acute or chronic conditions as compared to the peripheral blood insulin concentration obtained via the subcutaneous injection.

2. The oral solid dosage form of claim 1, which provides a lowering of insulin of at least about 20%.

3. An oral dosage form comprising a dose of unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient, and which provides a ratio of portal vein to peripheral blood insulin concentration from about 2.5:1 to about 6:1.

4. The oral dosage form of claim 3, wherein said dosage form is solid.

5. An oral dosage form comprising a dose of unmodified insulin that achieves a therapeutically effective reduction in blood glucose after oral administration to human diabetic patients, the oral solid dosage form providing an insulin t_{max} at a time point from about 0.25 to about 1.5 hours after oral administration to said patients, at least about 80% of the blood glucose concentration reduction caused by said dose of insulin occurring within about 2 hours after oral administration of said dosage form.

6. An oral dosage form comprising a therapeutically effective amount of unmodified insulin, said dosage form upon pre-prandial oral administration to human diabetic patients causing the mean plasma glucose concentration in said patients to be reduced for the first hour after oral administration relative to a mean baseline (fasted) plasma glucose concentration in said patients.

7. An oral dosage form comprising a therapeutically effective amount of unmodified insulin, said oral dosage form upon pre-prandial oral administration provides a mean plasma glucose concentration which does not vary by more than about 40% for the first hour after oral

administration, relative to a mean baseline (fasted) plasma glucose concentration in said patients, where a meal is eaten by said patients within about one half hour of oral administration of said dosage form.

8. The oral dosage form of claim 7, which provides a mean plasma glucose concentration which does not vary by more than about 30% for the first hour after oral administration.

9. An oral solid dosage form comprising a dose of insulin that achieves an insulin t_{max} at a time point from about 0.25 to about 1.5 hours after oral administration to a human diabetic patient, and which upon preprandial administration to the patient provides effective control of blood glucose concentration in response to the ~~solid~~ meal as manifested by providing a plasma glucose concentration which does not vary by more than about 40% for the first hour after oral administration from the baseline (fasted) plasma glucose concentration in the patient, and which provides a return to baseline blood insulin levels in the patient no later than 4 hours after oral administration.

10. The oral dosage form of claim 9, wherein the insulin is a form of human regular insulin.

11. The oral dosage form of any of the preceding claims, wherein the oral dosage form is solid.

12. The oral dosage form of claim 11, wherein the oral dosage form is in the form of a tablet or capsule.

13. The oral solid dosage form of claim 11, wherein the dose of unmodified insulin contained in the dosage form is from about 50 Units to about 600 Units (from about 2 to about 23mg).

14. The oral solid dosage form of any of the preceding claims, wherein the dose of unmodified insulin is from about 100 Units (3.8 mg) to about 400 Units (15.3 mg) insulin.

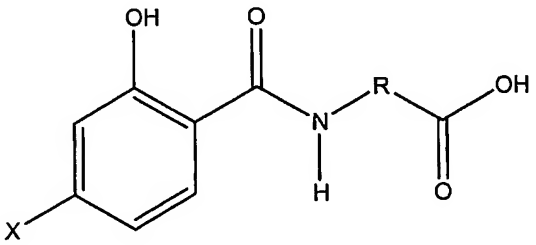
15. The oral solid dosage form of any of the preceding claims, wherein the dose of unmodified insulin is from about 150 Units (5.75 mg) to about 300 Units (11.5 mg).

16. The oral solid dosage form of claims 1-8, which provides a t_{max} for insulin at about 0.1 to about 1.5 hours after oral administration.

17. The oral solid dosage form of claim any of the preceding claims, which provides a t_{max} for insulin at about 0.25 to about 0.5 hours after oral administration.

18. The oral solid dosage form of any of the preceding claims, wherein the dosage forms begin delivering insulin into the portal circulation (via absorption through the mucosa of the stomach) to achieve peak levels within about 30 minutes or less.

19. The oral solid dosage form of any of the preceding claims, further comprising an effective amount of a delivery agent of the formula or a pharmaceutically acceptable salt thereof,



wherein

X is hydrogen or halogen;

R is substituted or unsubstituted C_1-C_3 alkylene, substituted or unsubstituted C_1-C_3 alkenylene, substituted or unsubstituted C_1-C_3 alkyl (arylene), substituted or unsubstituted C_1-C_3 aryl (alkylene).

20. The oral solid dosage form of claim 19, wherein X is a halogen.

21. The oral solid dosage form pharmaceutical composition of claim 20, wherein said halogen is chlorine.

22. The oral solid dosage form of claim 19, wherein R is C_3 alkylene.

23. The oral solid dosage form of claim 19, wherein said peak plasma delivery agent concentration occurs within two hours of oral administration.

24. The oral solid dosage form of claim 19, wherein said delivery agent is 4-[(4-chloro, 2-hydroxybenzoyl)amino]butanoic acid.

25. The oral solid dosage form of claim 19, which provides a peak plasma delivery agent concentration that is from about 5,000 and about 15,000 ng/ml within about 0.3 to about 1.5 hours after oral administration.

26. The oral solid dosage form of claim 19, which produces a maximal decrease in blood glucose in treated patients from about 20 and 60 minutes post oral administration.

27. The oral solid dosage form of claim 19, which produces a maximal decrease in blood glucose in treated patients at about 40 minutes post oral administration.

28. The oral solid dosage form of any of the preceding claims, wherein said composition produces a maximal decrease in C peptide concentration in treated patients from about 80 and 120 minutes post oral administration.

29. The oral solid dosage form of any of the preceding claims, which produces a lowered serum glucose in human patients by at least 10% with in one hour post oral administration.

30. A method of treating impaired glucose tolerance, achieving glucose homeostasis, treating early-stage diabetes, or treating late-stage diabetes, comprising administering the oral dosage form of any of the preceding claims on a chronic basis to human patients.

31. A method of providing a therapeutically effective orally administrable unit dose of unmodified insulin, comprising combining from about 2 to about 23 mg of unmodified insulin with from about 100 to about 600 mg of a pharmaceutically acceptable delivery agent which

facilitates absorption of said insulin from the gastrointestinal tract of human diabetic patients, and orally administering said unit dose to a human diabetic patient to provide a therapeutic effect.

32. A method of treating a human diabetic patient, comprising orally administering an oral dosage form comprising an effective dose of insulin pre-prandially to a human diabetic patient, such that an insulin tmax at a time point from about 0.25 to about 1.5 hours after oral administration is attained and blood glucose concentration of the patient is effectively controlled in response to the meal as manifested by providing a plasma glucose concentration which does not vary by more than about 40% for the first hour after oral administration from the baseline (fasted) plasma glucose concentration in the patient, and which provides a return to baseline blood insulin levels in the patient no later than 4 hours after oral administration.

33. The method of claim 3, wherein the insulin included in said oral dosage form is a form human regular insulin.

34. A method of treating diabetics, comprising orally administering to diabetic patients on a chronic basis an oral insulin treatment comprising a dose of unmodified insulin together with a delivery agent that facilitates the absorption of the insulin from the gastrointestinal tract to provide a therapeutically effective reduction in blood glucose and a peak blood plasma insulin concentration that is reduced relative to the peak blood plasma insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

35. The method of claim 35, wherein the incidence of a disease state associated with chronic insulin administration is reduced.

36. A method of treating diabetes and reducing the incidence and or severity of hyperinsulinemia associated with chronic dosing of insulin, comprising orally administering on a chronic basis to a diabetic patient a dose of insulin and a delivery agent that facilitates the

absorption of the dose of insulin from the gastrointestinal tract to provide therapeutically effective control and/or reduction in blood glucose concentrations, and a mean systemic blood insulin concentration of the diabetic patient that is reduced relative to the mean systemic blood insulin concentration provided by subcutaneous injection of insulin in an amount effective to achieve equivalent control and/or reduction in blood glucose concentration in a population of human diabetic patients.

37. A method of reducing the incidence and/or severity of one or more disease states associated with chronic administration of insulin, comprising treating diabetic patients via oral administration on a chronic basis with a therapeutically effective dose of a pharmaceutical composition which comprises insulin and a delivery agent that facilitates the absorption of insulin from the gastrointestinal tract, such that the pharmaceutical composition provides a therapeutically effective reduction in blood glucose and a peak serum insulin concentration of the diabetic patient that is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

38. The method of claim 34-37, wherein the method provides a reduced expression of genes associated with vascular disease as compared to the level of expression of genes associated with vascular disease resulting from an equivalent reduction in blood glucose concentration achieved in a population of patients via subcutaneous injection of insulin.

39. The method of claim 38, wherein the genes associated with vascular disease are selected from the group consisting of early response genes, genes associated with cytokines, genes associated with adhesion molecules, genes associated with lipid peroxidation, genes associated with thrombosis and combinations thereof.

40. The method of claim 39, wherein the early response genes are selected from the group consisting of c-myc, jun B, Egr-1, Ets-1 and combinations thereof.

41. The method of claims 34-37, wherein plasminogen activator inhibitor concentrations resulting from the method are lower as compared to the plasminogen activator inhibitor concentrations resulting from an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

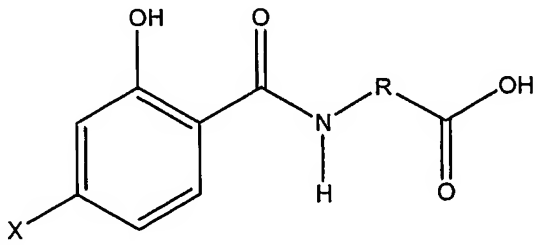
42. The method of claims 34-37, wherein the pro-inflammatory cytokine concentrations resulting from the method are lower as compared to the pro-inflammatory cytokine concentrations resulting from an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

43. The method of claims 34-37, wherein the disease state is cardiovascular disease.

46. The method of claims 34-37, wherein the disease state is selected from the group consisting of a neuropathy, a nephropathy, a retinopathy, an arteriopathy, atherosclerosis and combinations thereof.

47. The method of claims 34-37, wherein the disease state is selected from the group consisting of coronary artery disease, hypertensive cardiomyopathy and congestive heart failure.

48. The method of claims 34-37, wherein the delivery agent is a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

X is a halogen or hydrogen;

R is substituted or unsubstituted C_1-C_{12} alkylene, or a substituted or unsubstituted C_1-C_{12} alkenylene.

49. The method of claim 48, wherein the delivery agent is 4-[(4-chloro, 2-hydroxybenzoyl)amino-butanoic acid or a derivative or analog thereof.

50. The method of claims 34-37, wherein the insulin is selected from the group consisting of recombinant human insulin, bovine insulin, porcine insulin and functional equivalents thereof.

51. A method of treating diabetes and reducing the incidence and or severity of hyperinsulinemia associated with chronic dosing of insulin, comprising orally administering on a chronic basis to a diabetic patient a dose of insulin and a delivery agent that facilitates the absorption of the dose of insulin from the gastrointestinal tract to provide a therapeutically effective reduction in blood glucose and a peak serum insulin concentration of the diabetic patient that is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

52. A method of screening a drug for vascular injury associated with route of administering the drug, comprising

administering a drug to a first test animal parenterally;

administering the drug to a second test animal orally, and

comparing the expression of early response genes selected from the group consisting of c-myc, c-fos, Jun B, Erg-1 and combinations thereof for the first and second test animal, wherein an increase in the expression of one or more early response genes is indicative of vascular injury.

53. The method of claim 52, wherein the step of measuring the change in expression comprises gene chip analysis.

54. The method of claim 52, wherein the step of measuring the change in expression comprises measuring the changes in mRNA expression.

55. A method of reducing the incidence of, the severity of, or the incidence and severity of disease states or vascular diseases associated with chronic insulin administration to diabetics, comprising orally administering an oral insulin treatment comprising a dose of insulin together with a delivery agent which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a desired amount, such that the concentration of insulin circulating in the blood of said diabetic patients as a result of insulin treatment is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

56. A method of reducing the exposure of the vasculature of diabetic patients to hyperinsulinemic conditions, comprising orally administering an oral insulin treatment comprising a dose of insulin together with a delivery agent which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a desired amount, such that the concentration of insulin circulating in the blood of said diabetic patients as a result of insulin treatment is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration achieved by subcutaneous injection of insulin.

57. A method of attenuating processes resulting from the reaction to a mild injurious stimulus in multiple areas of the response to increases in mRNA during insulin treatment, comprising orally administering an oral insulin treatment comprising a dose of insulin together with a delivery agent which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a desired amount, such that the concentration of insulin circulating in the blood of said diabetic patients as a result of insulin treatment is reduced relative to the peak serum insulin concentration of an equivalent therapeutically effective reduction in blood glucose concentration

achieved by subcutaneous injection of insulin.

58. A method of treating diabetic patients, comprising orally administering an oral insulin treatment comprising a dose of insulin together with a delivery agent which facilitates the absorption of said insulin from the gastrointestinal tract on a chronic basis to diabetic patients to reduce blood glucose levels in said diabetic patients by a desired amount, such that the concentration of insulin circulating in the blood of said diabetic patients as a result of said oral insulin treatment is not substantially greater than normal physiological levels.